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Symptom Clusters and Quality of Life Trajectories in Breast Cancer Patients Before and After Chemotherapy

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Service Learning Capstone Experience Proposal

Title: Symptom Clusters and Quality of Life Trajectories in Breast Cancer Patients Before and After Chemotherapy

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Service-Learning Placement Site

The University of Nebraska Medical Center (UNMC) College of Nursing has an extensive and colorful history. The vibrant, bustling campus is situated in the heart of midtown Omaha. From the first class, which started in 1917, to the present day, College of Nursing alumni have been in the forefront of the evolution of the profession of nursing in Nebraska and in the nation and internationally (UNMC College of Nursing, 2017).

With 1,135 students currently enrolled, it is the prime nursing program in the state of Nebraska with five campuses: Kearney, Lincoln, Norfolk, Omaha, and Scottsbluff (UNMC College of Nursing, 2017).

The bachelor's, master's, and Doctor of Nursing Practice degree programs at the UNMC College of Nursing is accredited by the Commission on Collegiate Nursing Education, One Dupont Circle, NW, Suite 530, Washington, DC 20036, (202) 887-6791 (UNMC College of Nursing, 2017). The Ph.D. in Nursing program is part of the Graduate College at UNMC.

Mission

The mission of the College of Nursing is to transform lives through premier nursing education, innovative research, the highest quality health care, and promotion of health equity.

Vision

The vision of the College of Nursing is to be a vital contributor to a world-renowned health sciences center and to:

- advance innovative nursing education incorporating evidence-based experiential and active learning approaches;

- lead health care and health systems solutions based on world-class nursing research;
- promote health, reduce the burden of illness, and foster health equity in Nebraska and beyond; and,
- embrace diversity and inclusivity as essential to excellence.

Service Learning activities

1) Breast Cancer Collaborative Registry Study

The Breast Cancer Collaborative Registry (BCCR)[2] is a multicenter web-based system that was established at the University of Nebraska Medical Center (UNMC) Eppley Cancer Center (now Fred & Pamela Buffett Cancer Center). The BCCR is a resource that aims to facilitate the uniform collection of critical information by a questionnaire and blood sample to be used to develop new strategies for prevention and treatment of Breast Cancer (BC) and to improve Quality of Life (QOL). Using questionnaires and blood samples from current and new BCCR participants, we plan to increase knowledge of the etiology of sleep-wake disturbances that occur during and after BC treatment.

a. Data cleaning, data merging and running the analysis.
b. We will examine the association between the PSQI sleep index with the Sleep /Circadian gene SNP status using an ANOVA. Used SPSS to generate frequency tables for the gene polymorphisms, chromosome, and genotypes.
c. Hardy-Weinberg Equilibrium calculation was done. The Hardy-Weinberg equilibrium is a principle stating that the genetic variation in a population will remain constant from one generation to the next in the absence of disturbing factors. When mating is random in a large population with no disruptive circumstances, the

law predicts that both genotype and allele frequencies will remain constant because they are in equilibrium.

d. Attended the focused group meeting to keep up-to-date and report the progress of the project.

2) Mind and Brain Health Lab

Study title: Electrophysiological biomarkers of chemotherapy-related cognitive impairment and recovery.

The goal of this study is to better understand the influence of chemotherapy treatment on the neural mechanisms of attention and cognition.

a. Identifying eligible patients for the present study and interviewing the potential patient to obtain consent to enroll in the study.
b. Visit Oncology department at Fred & Pamela Buffet Cancer Center and Nebraska Medicine at Village to meet the eligible patient in the OPD.
c. Training of Apollo to get access to One Chart.

Service-Learning Goals and Objectives:

1. Goal #1: Satisfy service learning requirement.
    a. Objective: Analysis of BCCR study
        i. Activity #1: Getting data as Excel sheets
        ii. Activity #2: Merging the data and “cleaning” it.
        iii. Activity #2: Running the analysis and interpretation.

b. Objective: Assist in Chemo brain study

i. Activity #1: Going through the protocol of the study

ii. Activity #2: Training for One Chart Access

iii. Activity #3: Helping in identifying the potential patient for the study.

Activity #4:Observing recruitment of patients for the study.

Capstone Experience Goals and Objectives:

1. Goal #2: Application for Institutional Review Board (IRB).
    a. Objective: Ensuring privacy, confidentiality, security, and conflict of interest
        i. Activity #1: Filling the application and submitting it to the Institutional Review Board.
2. Goal #3: Analyzing data
    a. Objective: Run statistical analyses of the data.
        i. Activity #1: Importing all data from a previously filled Microsoft Excel spreadsheet into SPSS (Version 23), a computer package for statistics, to make analyses more practical.
        ii. Activity #2: Interpretation of the analyzed data.
2. Goal # 4: Report results of service learning and capstone experience activities.
    a. Objective: draft final paper.
        i. Activity #1: Create tables and figures to summarize the data.
        ii. Activity #2: Compose results and discussion section.
        iii. Activity #3: Submit a draft paper to the committee for the feedback.
        iv. Activity #4: Incorporate committee feedback to produce the final version.

b. Objective: Deliver an oral presentation

    i. Activity #1: Prepare PowerPoint slides for the oral presentation.

    ii. Activity #2: Deliver the presentation.

Abstract

Context. Breast cancer patients experience multiple concurrent symptoms before and after chemotherapy (CTX). Physical and psychological symptoms may persist after treatment and reduce the quality of life (QOL) of survivors.

Objectives. Identify differences in prevalence and severity of symptoms at three times within 1-year of starting CTX; and identify symptom cluster and QOL trajectories over these times in breast cancer patients.

Methods. Symptoms were identified in breast cancer patients (N=219) before the start of CTX (baseline), 30 days after the last CTX, and 1-year after the first CTX. Hospital Anxiety and Depression Scale and Symptom Experience Scale measured symptoms. The MOS-SF-36v2 questionnaire measured QOL. Exploratory factor analysis (EFA) was performed to identify symptom clusters at each time, then clusters were compared over time.

Results. The prevalence and severity of 10 symptoms gradually decreased over time ($p<0.05$). Fatigue, sleep disturbance, and pain were the most prevalent symptoms and mild in severity; depression was the least prevalent. Two symptom clusters were identified at baseline and one at the other two times. The number and type of symptoms in each cluster differed over time. There was an improvement over time in both the physical and mental component scores of QOL ($p <0.01$).

Conclusions. Symptoms improved over time from baseline to 1 year. Symptom experience appears to be dynamic and symptom clusters differed over time. Despite these symptoms, women reported QOL similar to population norms 1-year after the first CTX treatment.

Key Words: Breast cancer, symptom, symptom cluster, chemotherapy, quality of life, oncology

Introduction

Breast cancer is the most common cancer among women in the United States (US). In 2018, it is estimated that among U.S. women, there will be nearly 266,120 new cases of invasive breast cancer, along with the incidence of 63,960 new cases of non-invasive (in situ) breast cancer (Siegel, Miller & Jemal, 2018). Breast cancer patients often receive adjuvant treatment after primary surgical management to decrease the risk of relapse and improve survival rates (Flatley & Dodwell, 2016). The cost-effective approach for treating breast cancer patients is by adjuvant chemotherapy (CTX) when indicated (Hsu et al., 2017) as it increases the overall survival and distant disease-free survival (DFS), lowers breast cancer-specific mortality, decreases risk of recurrence, and decreases risk of contralateral breast cancer (Burstein et al., 2014; Anampa, Mokowar, and Sparano, 2015). CTX is most effective when the full dose and cycle of drugs are delivered in a timely manner, without significant delays in starting treatment (American Cancer Society, 2015).

Even with improving survival rates, breast cancer remains a major public health problem because of the multiple concurrent symptoms experienced by cancer survivors. Breast cancer survivors (BCS) are affected by adverse physical (i.e. fatigue, pain, and sleep disturbances) and psychological symptoms (i.e. anxiety, cognitive disturbances, depression). These symptoms frequently are present in the initial period after diagnosis and may persist many years thereafter; thus, reducing the quality of life (QOL) and functioning (Reich et al., 2017; Miaskowski, 2017). Symptoms tend to cluster together and may have natural associations, similarly shared pathways, and underlying mechanism (Francoeur, 2005; Reich et al., 2017; Sullivan et al., 2017). Dodd et el., (2001) defined a symptom cluster as two or more concurrent symptoms that are related to each other but are not required to share the same etiology.

Therefore, clinicians need to assess the symptoms as a cluster in addition to individually because symptoms in the cluster have a synergistic effect on morbidity, mortality, prognosis, and QOL (Miaskowski, Aouizerat, Dodd & Copper, 2007; Hsu et al., 2017).

Studies for symptom assessment often have used cross-sectional designs to measure symptoms at a single time point (Brant et al., 2011). Longitudinal studies have shown that symptoms may change over time (Huang, Chen, Liang & Miaskowski, 2014). Frequent symptoms assessments will broaden the understanding of symptoms experienced by women undergoing CTX for breast cancer (Hsu et al., 2017). Therefore, the use of a longitudinal study design that records symptoms at multiple time points is preferred (Sanford et al., 2014; Xiao, 2010). Due to multiple symptoms co-occurring in the breast cancer patients, we need to prioritize our investigation about symptom clusters.

Some longitudinal studies have examined symptom clusters at two times; before CTX and during CTX (Browall et al., 2014; Sanford et al., 2014; & Sullivan et al., 2018); before and after CTX or radiotherapy (Kim et al., 2008); and before and after surgery (Mazor et al., 2018). Only two studies have reported symptom clusters at three times; before, during and after CTX (Albusoul, Berger, Gay, Janson & Lee 2017; Phligbua et al., 2017). This paper extends the work of Albusoul et al (2017) by reporting on symptom clusters in the same sample before, 30 days after the last CTX, and 1-year after the first CTX. The research on symptom clusters in cancer has increased but remains limited and debatable.

A prospective longitudinal study design was used to obtain data before, during, and 1 month after the last CTX in Thai women (n=112) with breast cancer (Phligbua et al., 2013). The participants reported 39 symptoms at each time. Symptoms occurring most frequently over time were pain, worrying, I don’t look like myself, difficulty concentration, feeling irritable, hair loss,

lack of energy, taste changes and skin changes. Various symptom clusters by distress ratings were identfied at each time point; menopausal symptom, discomfort symptom,post-operative symptom,fatigue symptom and psycological symptom. Dynamic nature of the symptom exprerince was identified, while some of the specific symptoms within symptom cluster were relatively stable across all times.In the second study (Albusoul et al., 2017), researchers evlauted the symptom clusters before, during, and after the last CTX. They found that fatigue was the most prevalent symptom followed by sleep disturbance, pain, and concentration problem over the time points. Additionally, two symptom clusters were identified before and during CTX: gastrointestinal (GI) and treatment-related (Tr). However, only one reliable treatment-related symptom cluster consisting of fatigue, pain, and sleep disturbance was identified 30 days after the last CTX. Authors concluded that different symptom clusters were found before and after starting the CTX. However, the type and number of symptoms in each cluster were dynamic over time.

Due to improved screening and advances in the treatment of breast cancer, there has been a significant decrease in the mortality rate, allowing clinicians to focus on improvements in QOL and psychological well-being, rather than solely on life expectancy. The concept of QOL, which refers to the subjective assessment of a patient's health, is a major outcome measure in medicine, along with morbidity and mortality because it assesses a patient's subjective view of his or her health and serves as a prognostic factor (Brunault et al. 2016). Breast cancer survivors face several challenges to QOL, due in large part to the stresses of uncertainty surrounding a diagnosis of cancer and to adverse effects of adjuvant CTX and endocrine therapy (Demark et al., 2015).

Several studies have demonstrated that the physical and psychological syndromes associated with breast cancer patient treatments have a negative impact on their QOL (Sun, Hung, Yao, Lu & Chiang, 2016 & Cheng et.al 2016 & Paraskevi, 2012). QOL may decline significantly during

active cancer treatment and remain low for a short period thereafter. The majority of disease-free cancer survivors report good QOL 1-year post-treatment (Miller et al., 2016; Levkovich, Cohen, Pollack, Drumera & Fried, 2015; Ancoli-Israel et al., 2014 & Hsu et.al 2013).

Little is known about the long-term trajectory of the symptom clusters and of QOL. The studies that are available on cancer and its treatment-related symptoms are limited by either small samples, cross-sectional design, absence of baseline data, absence of long-term follow-up data, or no healthy controls (Ancoli-Israel et al., Hong-li et al., 2014; Xiao et al., 2016 & Ai et al., 2017). The last measurement of the studies of symptom clusters after CTX was 1-month post (Phligbua et al., 2013 & Albusoul et al., 2017). To our knowledge, no longitudinal studies were found that include baseline and measurements beyond 1 month after CTX.

Therefore, the aim of this study was to address the gaps in the literature of present knowledge to identify differences in prevalence and severity of symptoms at three times within 1-year of starting CTX; and identify symptom clusters and QOL trajectories over these times in breast cancer patients.

Methods

Study Design

This prospective, longitudinal study used secondary data from a randomized clinical trial known as "Fatigue in Breast Cancer: A Behavioral Sleep Intervention", funded by the National Institutes of Health and National Institute of Nursing Research (5R01NR007762-05). The aim of the primary study was to test the effectiveness of an Individualized Sleep Promotion Plan compared to a healthy eating control condition in women with breast cancer before, during, and after breast cancer adjuvant chemotherapy (Berger et al.,2009a, 2009b). This report extends the results of symptom clusters by Albusoul and reports on the clusters at three times: before, 30 days after the last CTX, and 1-year after the first CTX. The experimental and control groups were combined for the secondary data analysis as there were no statistically significant differences between the two groups on any of the independent variables at baseline or on any of the symptoms, including sleep, for T1 and T2 and for all dimensions of the symptoms. However, at T3 bowel pattern was different between the two groups. This finding was determined to be inconsequential because it was unlikely that CTX was the etiology of the bowel pattern many months since the last CTX. Therefore, bowel pattern was included in the analysis.

Sample and Settings

In the primary study, women with breast cancer (N=219) were recruited from two cancer centers and ten community oncology clinics in the Midwestern United States between April 2003 and May 2006. Inclusion criteria were: a) women 19 years and older; b) initial diagnosis of stages I to IIIA breast cancer; c) post-modified radical mastectomy or lumpectomy; d) scheduled to begin four anthracycline-based intravenous chemotherapy with or without taxane chemotherapy; e) English speaking; and f) Karnofsky Performance Scale (KPS) score greater than 60. Exclusion

criteria included comorbid diagnosis of chronic fatigue syndrome, unstable congestive heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, neuromuscular disease, sleep apnea, abnormal thyroid function, chronic steroid therapy, or working a job with rotating or permanent night shifts. The approvals of the Institutional Review Boards were obtained from all participating clinical sites. The available data decreased over time because of missing data or participants drop-out.

Variables and Instruments

Information on the symptoms was extracted from a variety of self-report questionnaires employed across the timeline: Hospital Anxiety and Depression Scale (HADS); Symptom Experience Scale (SES); and the Medical Outcomes Study, Short-Form Survey (MOS-SF 36 v2). For the present study, twelve variables were assessed: anxiety, depression, appearance, appetite, bowel pattern, concentration, fatigue, nausea, pain, sleep pattern, mental QOL component score, and physical QOL component score

After obtaining written informed consent from the patients, a baseline demographic questionnaire obtained information on age, education, marital status, menstrual status, ethnicity, race, employment status, working hours (weekly), body mass index (BMI), income, and activity level. Patient's medical records were reviewed for disease stage and treatment information. The functional performance at enrollment was measured with the Karnofsky Performance Scale based on the patients' self-report after explanation provided by the research nurse.

Instruments

Hospital Anxiety and Depression scale (HADS). The HADS is a 14-item self-assessment scale, with seven items measuring anxiety symptoms and seven measuring depression symptoms

(Zigmond & Snaith, 1983). The intensity of each symptom is measured by a four-point Likert scale. The total score for each symptom ranges from 0 to 21 and is interpreted as normal (0-7), mild (8-10), moderate (11-14), or severe (15-21). The questionnaire takes 2-5 minutes to complete (Stern, 2014). It has well-established validity and reliability (Bjelland, Dahl, Haug & Neckelma, 2002; Spinhoven, 1997). Internal consistency reliability (Cronbach's alpha) recommended level should be at least 0.60 for a self- report instrument to be reliable (Bjelland et al., 2002). In the current sample, internal reliability was estimated with Cronbach's alpha 0.85 for the anxiety and 0.80 for depression.

Symptom Experience Scale (SES). The SES measures women's symptoms associated with the treatment of breast cancer and each symptom measures for its frequency, intensity, and distress (Samarel et al., 1996). The scale consists of 24 items, rated on a five-point Likert scales from 0 (most positive result) to 4 (most negative result). Item scores are added to obtain total symptoms experience score, which ranges from 0 to 96; the higher the score, the greater the total negative symptoms experienced. This questionnaire can be completed in less than ten minutes. The scale is valid and reliable for measuring symptom experience in oncology patients. Internal consistency reliability was estimated with Cronbach's alpha and ranged between 0.66 and 0.74 in the current sample.

The Medical Outcomes Study, Short-Form Survey (MOS-SF 36 v2). A 36-item short-form (SF-36) was constructed to survey general health-related QOL (Goode et al.,2016). The SF-36v2 asks 36 questions to measure functional health and well-being from the patient's point of view. The SF-36v2 includes one multi-item scale that assesses eight health concepts: 1) physical functioning; 2) role physical; 3) bodily pain; 4) general health; 5) vitality; 6) social functioning; 7) role emotional; and 8) mental health (Ware, Kosinski, and Dewey, 2000). The eight multi-item

scales are aggregated into a physical component score (PCS) that measures the physical health status of the patient and a mental component score (MCS) that measures the patient's mental health status. The scale has established validity and reliability in patients with cancer (Costanzo et.al, 2007). The number of questions contributing to each domain varies from 2 to 10. Scores range from 0 (poorest health status) to 100 (best health status) (Ware, Kosinski and Dewey, 2000). US general population 1998 criterion, differentiate between healthy (≥50) and diseased QOL (<50) (Klinkhammer-Schalke, et al., 2008; ten Klooster et al., 2013; Lins & Carvalho, 2016). It usually takes 10-15 mins to complete all eight scales (Berger, Lockhart & Agrawal, 2009).

Data Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Appropriate descriptive statistics were calculated to summarize demographic and clinical characteristics at baseline, as well as the prevalence and severity of the individual symptoms at the different time.

An exploratory factor analysis (EFA) was conducted to identify the number of symptom clusters based on symptom severity at three times (Skerman, Yates, & Battistutta, 2012). EFA with principle axis factoring method (rotated component matrix with Promax rotation) was used to extract factors with an eigenvalue of 0.8. Given the exploratory nature of this study, cut-off criteria for factor loadings 0.3 was used to include the largest number of symptoms in the analysis to better represent the symptom experience of the study participants. A symptom cluster was accepted if symptom total correlations, with Cronbach's alpha (good ≥0.60 and poor <0.60) of ≥0.60. The value of Cronbach's alpha coefficient less than 0.60 was interpreted with cautions in the study. The best fit of symptom grouping was determined according to the following criteria: 1) simple

structure; 2) total variance explained by the symptom clusters, and 3) internal reliability of the symptom clusters measured by Cronbach α. as described by Albusoul et al. (2017).

Repeated-measures analysis was incorporated to calculate the mean score of PCS and MCS of QOL over time and compared to see the changes over time. Mauchly's sphericity test was used to validate a repeated measure analysis of variance (ANOVA). If the sphericity is violated, then Greenhouse-Geisser correction was used. For all the interpretation, a significance level of alpha of ≤ 0.05 (two-sided) was used.

Results

Demographic and Clinical Characteristics of Participants

The demographic and clinical characteristics of the participants are summarized in Table 1. The age of the participants ranged from 29 to 83 with a mean age of 52 years and the average BMI of 28.65 ± 6.10. Most patients were Non- Hispanic by ethnicity and white by race; the majority were married (72%) and had at least some post-secondary education (75%).

According to case records, most participants were diagnosed with Stage I and Stage II breast cancer. Approximately half of the women underwent modified mastectomy and rest had a lumpectomy. Most of the subjects were moderately active at baseline.

Symptoms Prevalence and Severity Trajectories Over Time

The symptom prevalence and severity at the three-times are summarized in Table 2. Fatigue was the most prevalent symptom followed by sleep disturbance and pain at all three times. Depression was the least prevalent symptom at each time point. Most of the symptoms were prevalent at baseline (T1) and gradually decreased at T2 and some of the symptom's prevalence diminished at T3. Symptoms with prevalence more than 20% were included for further analysis. Exclusions due to prevalence <20% were depression at T1, depression, and nausea at T2; and appetite, depression, nausea, and appearance at T3. were.

The mean symptom severity score for the SES symptoms ranged from lowest (appetite) to highest (fatigue) across all time. At baseline, mean symptom severity of pain, sleep disturbance, and fatigue was highest. Fatigue was the only symptoms that had a severity mean greater than 1.00 at all time . Pain and sleep disturbance mean severity score were similar when compared from T2 to T3. Fatigue, concentration and appearance severity mean were highest at 30 days after the last CTX than at baseline and 1-year after the last CTX. The mean severity scores for anxiety and

depression were within normal range (<7) at each time. However, anxiety score was highest at baseline and gradually decreased over time. Depression score was highest at T2, was lower at T1, and lowest at T3. For appetite and appearance, Mauchly's test of sphericity was violated; therefore Greenhouse-Geisser correction was used for the further interpretation.

Overall, there was a statistical difference ($p<0.05$) in the mean score of all the symptoms over time, suggesting that the prevalence and severity of symptoms decreased over time. However, symptoms of fatigue, sleep disturbance, pain, concentration, bowel pattern, and anxiety were still prevalent 1- after year the first CTX. Although prevalent, symptom severity was reported as mild.

Symptom Clusters at Each Time and Trajectories Over Time

Time 1

At baseline, two viable symptom clusters were identified. The first cluster was labeled a treatment-related (Tr) SC and consisted of three symptoms: sleep disturbance, concentration, and anxiety. A second cluster was labelled gastrointestinal (GI) SC and consisted of four symptoms: nausea, pain, fatigue and bowel pattern (Tables 3 and 4). Cronbach's α ranged from 0.62─0.70, indicating good internal consistency reliability.

Time 2

Only one reliable Tr SC was identified 30 days after the last CTX. The Tr SC consisted of four symptoms: fatigue, sleep disturbance, pain, and concentration with good internal consistency reliability of 0.68. Two new symptoms were added (fatigue and pain) to Tr SC to T2 when compared from baseline. Anxiety and nausea dropped out, compared to baseline. A second GI SC consisted of three symptoms: concentration, appearance, and anxiety but had poor internal consistency reliability ($\alpha=0.59$), and therefore was not considered viable.

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Time 3

One Tr SC was identified 1-year after the first CTX. Tr SC consisted of pain, sleep disturbance, fatigue, concentration and anxiety with good internal consistency reliability of 0.73. Tr SC at T3 were similar to the Tr SC at T2, but anxiety returned at T3. A GI SC consisted of pain and bowel pattern (Table 3), but it had internal consistency reliability of 0.58, thus was not considered reliable.

The symptom experience was dynamic, thus the types and number of symptoms included in each cluster was somewhat variable. However, symptoms in the Tr SC were quite similar over time; each one was included at least two of the three times. Interesting the Tr SC at 1-year after the first CTX had highest number of symptoms included in the cluster with highest variance and Cronbach's value.

Quality of Life over time

Scores on the eight QOL scales improved over time (Table 5). Before starting CTX (T1), vitality was lowest while role emotional scale was highest, followed by social functioning. At 30 days after the last CTX (T2), role emotional was highest, followed by mental health and social functioning, while vitality was still lowest. At 1-year after the first CTX (T3), social functioning was highest, followed by role emotional, physical functioning, and mental health. Vitality had the lowest score at each time. Role physical, followed by bodily pain and social functioning score significantly improved over time.

Two QOL component scores, PCS and MCS improved over time (Figure 1). Repeated measures indicated that there was a statistically significant difference in the mean component scores over time. QOL of the breast cancer participants improved at 1-year after the first CTX compared to the baseline but the PCS remained lower than the population norm score.

Discussion

This study is the first to examine the trajectories of symptoms clustered by severity in breast cancer patients at baseline, 30 days after the last CTX and 1-year after the first CTX. Additionally, the present study reports that the symptom prevalence and severity mean decreased over time but even 1-year after the first CTX, several symptoms were prevalent at a mild level. We identified the dynamic nature of symptoms and symptom clusters in the present study. However, treatment-related symptom cluster was relatively stable at three times. Physical and mental health domains of QOL improved over time and were similar to the population norm 1-year after the first CTX.

At baseline, breast cancer patients reported experiencing several symptoms. The top five based on severity were: fatigue, sleep, pain, concentration, and anxiety. This result was similar to the report by (Phligbua et al., 2017). The high prevalence of symptoms at baseline could be due to recent diagnosis and surgical procedure. At 30 days after the last CTX, the prevalence of the symptoms was high and was similar to the study by Phligbua et al., 2017. Persistent symptoms could be due to recent CTX and fear of recurrence of cancer. Surprisingly, in our study, depression was the least prevalent symptom. Symptom prevalence and severity decreased over time but even at 1-year after the first CTX, some symptoms (fatigue, sleep disturbance, pain, concentration, pattern and anxiety) were still present >20% of the sample. This may be because the participant's mean age was 52 years and may be experiencing post-menopausal symptoms. They also may be experiencing other age-related diseases (arthritis and osteoporosis) and side effects related to oral endocrine therapy prescribed for the women diagnosed with estrogen/progesterone receptor-

positive breast cancer. Report by the studies (Huang et al., 2014 & Sanford et al., 2014) was similar to our result that there was gradual decrease in the symptom prevalence and severity over time.

Before initiating CTX, two symptom clusters (Tr and GI) were identified by severity domain. Tr SC comprised of three symptoms: sleep disturbance, concentration, and anxiety, while GI SC comprised of four symptoms: fatigue, pain, bowel pattern, and nausea. Our results were similar to the other studies (Kim et al., 2008; Phligbua et al., 2017; Browell et al., 2014 & Chongkham-ang et al., 2018) and indicate that this could be due to recent surgery or diagnosis in the patients. At 30-days after the last CTX, we found one reliable symptom cluster with four symptoms: fatigue, sleep disturbance, pain, and concentration. Our finding was similar with Phligbua et al.'s findings; the symptoms like sleep disturbance, pain, and concentration clustered together. These finding could be the effect of recent completion of CTX. Another potential cluster was borderline with a Cronbach's α of 0.59 and results need to be addressed cautiously. It could be due to the low item-total correlation of appearance which changed the Cronbach's α.

At 1-year after the first CTX, one cluster was observed; consisting of five symptoms: fatigue, sleep disturbance, pain, concentration, and anxiety. Another potential GI was not considered reliable due to low Cronbach's α 0.58. This could be due to few symptoms meeting our inclusion criteria for the factorial analysis at 1-year after the first CTX. It was surprising to see that depression prevalence was < 20% in our study population at each time. We used the same database of the Albusoul et al., 2017, and tried to extend their work to better understand the trajectories of the symptom clusters and symptoms prevalence by severity domain at 1-year after the first CTX. The differences in the symptom clusters over 1-year may be due to acute effects of CTX as some symptoms' prevalence decreases <20% after the completion of CTX. The dynamic nature of the

number and make-up of symptom clusters were supported by other studies (Kim et al., 2008; Browell et al., 2014; Phligbua et al., 2017; Albusoul et al., 2017 & Chongkham-ang et al., 2018).

The QOL PCS and MCS domains were below the general population at baseline. This result was consistent with reports by Paraskevi, 2012; and Ai et al., 2017. These women experience at least some psychosocial distress during the course of their diagnosis. Even at 30 days after the last CTX, PCS and MCS were below the general population. The result was consistent with the report of Paraskevi, 2012, as fear of recurrence is a commonly dominant emotion that is difficult to control. MCS at 1- year after the last CTX just was over the normal general population, indicating good QOL. Repeated measures show that PCS and MCS improved over the 1-year time. This could be explained as QOL becomes better as the prevalence of the symptoms decreases over time.

There are several limitations of this study which are important to consider when interpreting the results. One of the biggest limitations of this study is that data obtained for the analysis was outdated because of a lag time between data collection and the proposed secondary data analysis. The present study uses a secondary data set which is descriptive in nature; therefore, it is difficult to examine causality. Another major flaw in this study is due to a limited number of symptoms included in the database. Other studies (Phligbua et al., 2013 & Chongkham-ang et al., 2018) included 32 to 39 symptoms in their analysis and there were only 10 symptoms in this analysis. Additionally, symptoms were measured by a non-specific symptom scale and there could be lower response validity because the symptom name could be misinterpreted by the patients.

Conclusions

Despite the limitations, our study will aid in the development of effective interventions to minimize symptom clusters and improve QOL in breast cancer patients. Healthcare professionals need to assess the symptom experience and QOL before. During, and after CTX in breast cancer patients as there are limited numbers of longitudinal studies. Our study reports about the co-occurrence of a symptom with aother helps to better understand symptom clusters in breast cancer survivors. After identifying the symptom prevalence, symptom clusters, and QOL oncology team can refer patients to relevant specialized healthcare professionals. Future studies of symptom clusters in patients with breast cancer need to evaluate the stability of symptom clusters over time. In addition, research is needed on the number and types of symptom clusters that occur prior to the initiation and after the CTX. Future studies should evaluate the efficacy of symptom management strategies for specific symptom clusters in patients with breast cancer who have undergone CTX.

Table 1

Demographic and Clinical Characteristics of the Sample at Baseline (*n*=219)

Characteristic		Mean (SD)
Age, yrs.		52.15 (9.98)
Working hours/week		28.27 (18.96
Body mass index, kg/m^2		28.65 (6.10)
		N (%)
Ethnicity		
	Hispanic	8 (3.7)
	Non- Hispanic	211 (96.3)
Race		
	White	209 (95.4)
	Non- White	10 (4.6)
Education		
	Up to high school	55 (25.1)
	Some college or more	164 (74.9)
Marital status [a]		
	Married	158 (72.1)
	Non-Married	61 (27.9)
Employment status		
	Employed	163 (74.4)
	Non- Employed	56 (25.6)
Household income (annual)		
	Less than $20,000	21 (9.6)
	$ 20,000 - $40,000	45 (20.5)
	>$ 40,000	145 (66.2)
Surgical procedure		
	Lumpectomy	95 (43.4)
	Modified mastectomy	123(56.2)
Breast cancer stage		
	Stage I	72 (32.9)
	Stage II	114 (52.1)
	Stage IIIA	31 (14.2)
Menstrual status		
	Regular	69 (31.5)
	Irregular	143 (65.3)
Karnofsky score		
	60-70	10 (4.6)
	80-100	209 (95.4)
Activity level		
	Moderately active	195 (89.0)
	Non- Active	24 (11.0)

n, number; SD, standard deviation.
[a] Not married includes single or never married, separated, divorced or widowed.
Not all columns add up to n=219 due to missing value.

Table 2

Symptom Prevalence and Severity at three-time

Symptoms	Baseline (T1)		30 days after last CTX (T2)		1 yr. after the first CTX (T3)		
	Prevalence (%)	Severity Mean (SD)	Prevalence (%)	Severity Mean (SD)	Prevalence (%)	Severity Mean (SD)	P value
Nausea*	**23.2**	0.32 (0.68)	13.9	0.16 (0.44)	11.5	0.16 (0.50)	0.02
Pain*	**79.0**	1.28 (0.79)	**60.9**	0.88 (0.86)	**60.2**	0.88 (0.88)	<0.01
Appetite*	**39.4**	0.45 (0.62)	**27.9**	0.34 (0.62)	7.5	0.12 (0.47)	<0.01
Sleep Disturbance*	**79.4**	1.25 (0.91)	**62.0**	0.90 (0.89)	**63.1**	0.90 (0.86)	<0.01
Fatigue*	**89.8**	1.21 (0.64)	**94.5**	1.32 (0.64)	**87.2**	1.2 (0.68)	0.03
Bowel Pattern*	**35.8**	0.46 (0.70)	**29.0**	0.37 (0.64)	**24.3**	0.31 (0.58)	0.03
Concentration*	**54.5**	0.66 (0.69)	**59.4**	0.74 (0.71)	**43.4**	0.53 (0.68)	<0.01
Appearance*	**23.7**	0.26 (0.49)	**33.4**	0.42 (0.70)	12.7	0.14 (0.40)	<0.01
Anxiety**	**38.3**	6.58 (3.87)	**22.4**	4.62 (3.75)	**23.2**	4.69 (3.61)	<0.01
Depression**	10.9	3.25 (3.00)	13.5	3.99 (3.28)	9.8	2.52 (2.71)	<0.01

** The scores range from 0 (most positive result) to 4 (most negative result),*
***The scores range from 0 (least severe) to 21 (most severe).*

Table: 3

Factor loading scores of Symptom Clusters (n=202)

Symptoms	Tr SC	GI SC	GI SC (1)	Item-total r Factor 1	Item-total r Factor 2
Baseline					
Nausea	-0.17	**0.48**	0.15		0.36
Appetite	-0.05	0.22	**0.54**		
Bowel pattern	0.05	**0.45**	-0.01		0.34
Pain	0.04	**0.54**	0.03		0.42
Fatigue	0.17	**0.57**	0.06		0.46
Sleep Disturbance	**0.55**	0.21	-0.14	0.45	
Concentration	**0.71**	-0.17	0.26	0.52	
Anxiety	**0.74**	-0.03	-0.10	0.54	
Appearance	0.29	0.27	0.04		
Baseline SC total					
Cronbach α				0.70	0.62
Variance (%)	28.30	7.08	2.56		
T2					
Fatigue	**0.60**	0.003	0.09	0.52	
Sleep disturbance	**0.62**	-0.11	0.05	0.43	
Pain	**0.68**	-0.13	-0.04	0.41	
Concentration	**0.36**	**0.38**	-0.11	0.40	0.44
Appearance	-0.25	**0.66**	0.09		0.31
Anxiety	0.29	**0.46**	-0.05		0.46
Appetite	0.02	0.04	**0.73**		
Bowel Pattern	0.28	0.08	0.27		
T2 SC total					
Cronbach α				0.66	0.59
Variance (%)	26.78	6.39	5.29		
T3					
Pain	**0.39**	**0.32**		0.48	0.40
Sleep disturbance	**0.40**	0.22		0.42	
Fatigue	**0.52**	0.09		0.44	
Bowel pattern	-0.08	0.82			0.40
Concentration	**0.64**	-0.08		0.47	
Anxiety	**0.75**	-0.08		0.55	
T3 SC total					
Cronbachα				0.73	0.58
Variance (%)	34.25	7.38			

SC= symptom cluster; Tr SC =treatment related symptom cluster; GI = gastrointestinal symptom cluster (at T2 two GI SC were identified)
Not all columns add up to n=202 due to missing value.

Table 4

Overall Symptom clusters over 1-year

Symptom Clusters	Baseline (T1)	30 days After last CTX (T2)	1-year after Baseline (T3)
Tr SC	**Sleep Disturbance** **Concentration** **Anxiety**	**Fatigue** **Sleep Disturbance** **Pain** **Concentration**	**Fatigue** **Sleep Disturbance** **Pain** **Concentration** **Anxiety**
Variance (%), α	28.30, 0.70	26.78, 0.68	34.25, 0.73
GI SC	**Fatigue** **Pain** **Bowel Pattern** **Nausea**	*Concentration* *Appearance* *Anxiety*	*Pain* *Bowel Pattern*
Variance (%), α	7.08, 0.62	6.39, 0.59	7.38, 0.58
Total Variance (%)	35.38	26.78	34.25

SC= symptom cluster; Tr SC =treatment related symptom cluster; GI = gastrointestinal symptom cluster

Table 5

SP-36v2 Health Survey: Eight Health Domain Scales and Physical Component Score and Mental Component Score at 3-time (n=205)

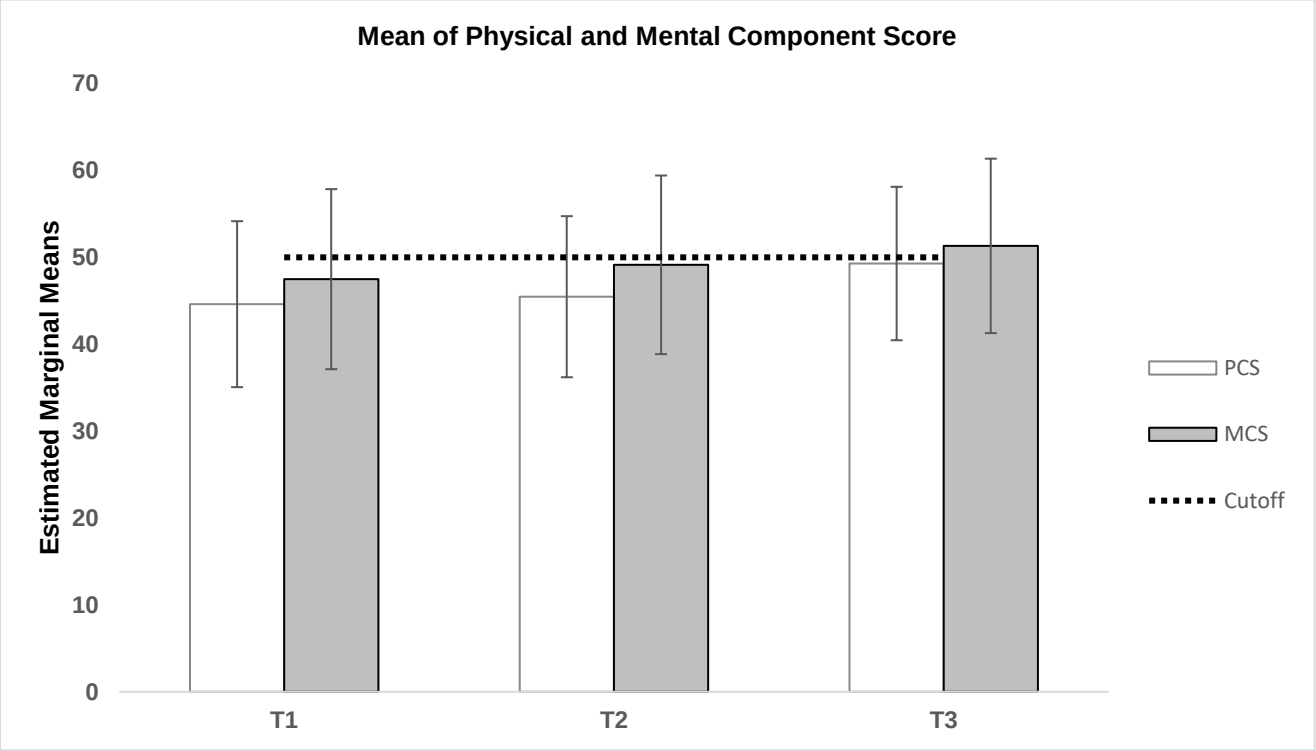
	Baseline	**30 days after the last CTX**	**1 year after the first CTX**	**p-value**
Scales ǂ	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Physical Functioning	70.62 (22.37)	70.24 (24.54)	80.51 (21.70)	<0.001
Role Physical	59.00 (27.97)	61.77 (26.70)	77.96 (23.71)	<0.001*
Bodily Pain	60.24 (23.29)	72.31 (24.21)	74.66 (23.16)	<0.001
General Health	70.98 (16.94)	70.02 (19.51)	74.57 (18.48)	0.003
Vitality	56.09 (20.07)	52.36 (21.32)	62.72 (20.92)	<0.001
Social Functioning	74.93 (23.57)	76.54 (23.19)	86.29 (18.72)	<0.001*
Role Emotional	76.76 (22.43)	78.95 (25.33)	82.94 (23.75)	0.009*
Mental Health	69.55 (17.59)	76.77 (17.43)	80.40 (15.76)	<0.001
Physical component score	44.61 (9.55)	45.47(9.27)	49.29(8.83)	<0.001
Mental component score	47.49(10.36)	49.14(10.28)	51.32 (10.04)	0.003*

ǂ *higher values indicate a higher level of functioning and quality of life (0-100).*

**Greenhouse-Geisser for the p-value as the Mauchly's test of sphericity was violated.*
Not all columns add up to n=205 due to missing value.

Figure 1

Quality of Life (SF-36 v2) physical and mental component score over 3 time-point



Note: T1: before starting the CTX; T2: 30 days after the CTX and T3: 1 year after the CTX

PCS=physical component score; MCS= mental component score; Cutoff= normal value of the QOL

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Service Learning/ Capstone Experience Reflection

College of Nursing at UNMC has advance innovative nursing education incorporating evidence-based experiential and active learning approaches. It promotes health, reduces the burden of illness, and foster health equity. Before starting the project, I didn't know that college of nursing has so many research opportunities. They have several research projects that have internal and external funds. The professors and staff were supportive and helpful. I am thankful to Dr. Ann Berger who have helped me a lot while doing this project.

My Service learning activities consisted of two parts. I worked on the Breast Cancer Collaborative Registry (BCCR) project to examine the association between the Pittsburg Sleep Quality Index (PSQI) and polymorphisms in sleep /circadian rhythm genes. I attended regular meetings, did a literature review, data cleaning, and data merging used SPSS to generate frequency tables for the gene polymorphisms, chromosome and genotypes and Hardy-Weinberg Equilibrium calculation. Second, I worked at the Mind and Brain Health Lab, where the goal of the study was to better understand the influence of chemotherapy treatment on the neural mechanisms of attention and cognition. Activities that I did in this project are training in Apollo to get access to One Chart, Identifying eligible patients for the study, visiting Oncology Department at Fred & Pamela Buffet Cancer Center and Nebraska Medicine at Village Pointe to meet eligible patients, and learn how to obtain the consent. The above activity was done under the supervision of Dr. Ann Berger and time spent in these activities were around 150hrs.

During my service learning activities, I tried to clean the databases and attempted to merge two databases (BCCR and PSQI), but we were only able to perform basic statistical analysis. I got an experience about work culture in clinical research.

Several challenges during the service learning and capstone activity were encountered. Some of them are that while working for the genetic analysis, it was difficult to merge the two databases but with help of my committee member we fixed the problem and merged the data. Further doing the genetic analysis, I had limited knowledge and Dr. LeVan helped me initial analysis like generating frequency table for the gene polymorphism, chromosomes and genotype. Additionally, we calculated Hardy-Weinberg Equilibrium, but the results were not appropriate to do further analysis. While doing a Capstone project, we had to select the appropriate statistical methods and that was solved with the help of committee members.

The service learning and capstone project have helped to improve my statistical and epidemiological skills. Along with writing skill and critical thinking. I believe that public health curriculum has prepared me to address the issues encountered during the above activity.

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